Guidance for Industry

Special Protocol Assessment

DRAFT GUIDANCE

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For questions on the content of the draft document, contact Murray M. Lumpkin, CDER, at 301-594-5400 or Robert A. Yetter, CBER, at 301-827-0373.

U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
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Table of Contents

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(Due to the complexity of this draft document, please identify specific comments by line number. Use the pdf version of the document whenever possible.)

I. INTRODUCTION

This document is intended to provide guidance to industry on procedures adopted by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) for evaluating issues related to the adequacy (e.g., design, conduct, analysis) of certain proposed studies associated with the development of products in human drug applications as defined in section 735(1) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 379g(1)) (PDUFA products). This guidance implements section 119(a) of the Food and Drug Administration Modernization Act (the Modernization Act) by describing procedures for sponsors to request special protocol assessment and for the Agency to act on such requests. For the purposes of this guidance document, the term *sponsor* includes any sponsor or applicant interested in special protocol assessment.

II. BACKGROUND

A. PDUFA Goals for Special Protocol Assessment

In conjunction with the reauthorization of the Prescription Drug User Fee Act of 1992 in November 1997 (PDUFA 2), FDA agreed to specific performance goals (PDUFA goals) for special protocol assessment and agreement. The PDUFA goals are described in the *PDUFA Reauthorization Performance Goals and Procedures*, an enclosure to a letter dated November 12, 1997, from the Secretary of Health and Human Services, Donna E. Shalala, to Senator James M. Jeffords.

The PDUFA goals for special protocol assessment and agreement provide that, upon request, FDA will evaluate within 45 days certain protocols and issues relating to the protocols to assess whether they are adequate to meet scientific and regulatory requirements identified by the sponsor. Three types of protocols related to PDUFA products are eligible for this special protocol assessment under the PDUFA goals: (1) animal carcinogenicity protocols, (2) final product stability protocols, and (3) clinical protocols for phase 3 trials whose data will form the primary basis for an efficacy claim if the

[1] This guidance has been prepared by the Review Management Working Group comprising individuals in the Centers for Drug Evaluation and Research (CDER) and Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on special protocol assessment and agreement. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

trials had been the subject of discussion at an end-of-phase 2/pre-phase 3 meeting with the review division or if the division is otherwise aware of the developmental context in which the protocol is being reviewed and the questions are being answered. The clinical protocols for phase 3 trials may relate to efficacy claims that will be part of an original new drug application (NDA) or biologics license application (BLA) or that will be part of an efficacy supplement to an approved NDA or BLA.

B. Modernization Act Provisions for Meetings and Agreements on Clinical Trials

Section 119(a) of the Modernization Act amends section 505(b) of the Act (21 U.S.C. 355(b)). New section 505(b)(4)(B) of the Act directs FDA to meet with sponsors, provided certain conditions are met, for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim in a marketing application submitted under section 505(b) of the Act or section 351 of the Public Health Service Act (42 U.S.C. 262).[2] Such marketing applications include NDAs, BLAs, and efficacy supplements to approved NDAs and BLAs.

Under new sections 505(b)(4)(B) and (C) of the Act, if a sponsor makes a reasonable written request to meet with the Agency for the purpose of reaching agreement on the design and size of a clinical trial, the Agency will meet with the sponsor and, if an agreement is reached, will reduce the agreement to writing and make it part of the administrative record. An agreement may not be changed by the sponsor or FDA after the trial begins, except (1) with the written agreement of the sponsor and FDA, or (2) if the director of the FDA reviewing division determines that "a substantial scientific issue essential to determining the safety or effectiveness of the drug" was identified after the testing began (section 505(b)(4)(C) of the Act). If a sponsor and the Agency meet regarding the design and size of a clinical trial under section 505(b)(4)(B) of the Act and the parties cannot agree that the trial design is adequate to meet the goals of the sponsor, the Agency will clearly state the reasons for the disagreement in a letter to the sponsor. However, the absence of an articulated disagreement on a particular issue may not be assumed to represent an agreement reached on that issue.

Meetings between the Agency and sponsors are generally helpful in reaching agreement on the design and, in some cases, interpretation of carcinogenicity studies, stability studies, and clinical trials.[3]

C. Focus of This Guidance

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[2] Section 119(b) of the Modernization Act directs FDA to meet with sponsors and applicants, provided certain conditions are met, to reach agreement on the design and size of bioavailability and bioequivalence studies needed to support applications submitted under section 505(j) of the Act (i.e., abbreviated new drug applications). FDA intends to issue a separate guidance document that will address the implementation of section 119(b) of the Modernization Act.

[3] In March 1999 (64 FR 13591), FDA made available for comment a draft guidance for industry, *Formal Meetings with Sponsors and Applicants for PDUFA Products*, describing policies and procedures that will be adopted by CDER and CBER to enhance the productivity of meetings between the Agency and sponsors of PDUFA products. Once the draft guidance is finalized, the procedures described in the guidance will promote the PDUFA performance goals for meeting management and section 505(b)(4)(B) of the Act. FDA intends to issue additional guidance describing CDER's and CBER's general procedures for formal meetings with sponsors of non-PDUFA products (including generic drug products).

Sections 505(b)(4)(B) and (C) of the Act and the PDUFA goals describe Agency procedures for evaluating certain protocols and working towards, and achieving, agreement with sponsors and applicants on the design and size of studies and clinical trials that may be used for approval of a drug or biological product. Unless otherwise stated, the procedures described in this guidance apply to special protocol assessment of carcinogenicity protocols, stability protocols, and clinical protocols for phase 3 trials whose data will form the primary basis of an efficacy claim. As the PDUFA goals for special protocol assessment are more comprehensive[4] and specific (e.g., they give specific times for Agency review) than the requirements of sections 505(b)(4)(B) and (C) of the Act, this guidance focuses on procedures to achieve the PDUFA goals. The requirements of section 505(b)(4)(B) and (C) of the Act will also be fulfilled by achieving the PDUFA goals for special protocol assessment.

III. REQUESTS FOR SPECIAL PROTOCOL ASSESSMENT

Under the PDUFA goals, FDA will evaluate certain protocols when the sponsor requests evaluation. A separate request should be submitted for each specific protocol the sponsor would like reviewed. The procedures for requesting special protocol assessment are described below.

A. Timing of Request

CDER and CBER generally recommend that a sponsor submit a protocol intended for special protocol assessment to the Agency at least 90 days prior to anticipated commencement of the study. The protocol should be complete and sufficient time should be allowed to discuss and resolve any issues before the study begins. *Special protocol assessment will not be provided after a study has begun.*

1. *Carcinogenicity Protocols*

A sponsor interested in Agency assessment and agreement on a carcinogenicity protocol should notify the appropriate review division (CDER) or applications division (CBER) and discuss planned carcinogenicity testing at an end-of-phase 2 meeting or should notify the director of the appropriate division of an intent to request special protocol assessment by letter at least 30 days prior to submitting the request. With the notice of intent, the sponsor should submit relevant background information so that the Agency may review (or re-review) reference material related to carcinogenicity protocol design prior to receiving the carcinogenicity protocol. The Agency is currently drafting guidance describing the type of information that would be appropriate to submit before requesting carcinogenicity protocol assessment.

2. *Stability Protocols*

Generally, an end-of-phase 2/pre-phase 3 meeting should take place between the sponsor and

[4] The PDUFA goals regarding clinical protocol review and assessment are wider in scope than section 505(b)(4)(B) of the Act. Both the noted statutory requirements and the PDUFA performance goals apply to protocols for clinical trials intended to form the primary basis of an effectiveness claim in original and supplemental applications. The PDUFA performance goals, however, *also* apply to animal carcinogenicity protocols and final product stability protocols, whereas the statutory section does not.

the Agency. Agreement on a standard stability protocol for primary stability batches may be reached in such a meeting. A new stability protocol significantly different from the standard stability protocol may be submitted to the Agency with a request for special protocol assessment. Prior to requesting special protocol assessment for a stability study, a sponsor should ensure that the product is sufficiently developed. The product should be in phase 3 development and product characterization should be complete. Production steps that may affect product stability should be identified. The sponsor should also ensure that the manufacturing process described in the request for assessment of the stability protocol will not differ substantively from the process used for marketed material and that the tests described will adequately qualify the product.

3. *Clinical Protocols*

As stated in the PDUFA goals, for special protocol assessment of a phase 3 protocol for a clinical trial that will form the primary basis of an efficacy claim in an NDA or BLA, the sponsor should have had an end-of-phase 2/pre-phase 3 meeting with the review division so that the division is aware of both the developmental context in which the protocol is being reviewed and the questions that are to be answered. However, if the Agency is already familiar with the developmental context of a proposed clinical trial and has an understanding of the questions that will be raised regarding the protocol, as ordinarily will be the case with efficacy supplements, the Agency may provide a comprehensive protocol assessment without requiring an end-of-phase 2/pre-phase 3 meeting.

B. Format of Request

A sponsor should submit each protocol for assessment under this program as a separate amendment to the sponsor's IND in triplicate with Form FDA 1571 and a cover letter attached. The cover letter should clearly identify the submission as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** in bolded block letters at the top and should clearly state the type of protocol being submitted (i.e., carcinogenicity, stability, or clinical).

C. Where to Send a Request

The request should be submitted to the appropriate review division in CDER or applications division in CBER. A copy of the cover letter should be sent via fax as follows.

For carcinogenicity protocols:

- in CDER, to the project manager for the application in the appropriate review division and the Associate Director for Pharmacology and Toxicology in the Office of Review Management
- in CBER to the director of the appropriate applications division

For stability protocols:

- in CDER, to the project manager for the application in the appropriate review division and the appropriate chemistry team leader
- in CBER, to the director of the appropriate applications division

For clinical trials intended to form the primary basis of an efficacy claim:

- in CDER, to the project manager for the application in the appropriate review division
- in CBER, to the director of the appropriate applications division

A sponsor interested in seeking special protocol assessment before submitting an IND should contact the chief of the project management staff in the appropriate review division in CDER or should submit a written request to the director of the appropriate applications division for the product in CBER. Sponsors who request special protocol assessment without an IND should note that the Agency will not be able to provide special protocol assessment without being fully informed of the overall development plan for the drug or biological product.

D. Content of a Request

In the request for special protocol assessment, the sponsor should pose focused questions concerning specific issues regarding the protocol, protocol design (including proposed size), study conduct, study goals, and/or data analysis for the proposed investigation. Although the questions should be specific to the protocol and should not address overall development strategies, the role of the study in the overall development plan needs to be clear to the Agency in order for it to answer the protocol-specific questions.

To facilitate FDA's assessment of the issues raised by the sponsor, a request should discuss in reasonable detail all data, assumptions, and information needed for an adequate evaluation of the protocol. For example:

- The sponsor should include information needed to assess the role of the study in the overall development of the drug.

- The sponsor should submit information supporting the proposed trial, including power calculations, the choice of study endpoints, and other critical design features (e.g., choice of control, duration, methods of assessment).

- The sponsor should clearly describe any regulatory outcomes (e.g., approval of a specific claim, breaking orphan exclusivity, a comparative claim) and final labeling that the sponsor believes would be supported by the results of the study.

- A sponsor interested in Agency assessment of a stability protocol should include product characterization and relevant manufacturing data, information regarding the proposed market packaging configuration (if known), the proposed drug product strengths, and the expected shelf-life.

Special protocol assessment is designed to evaluate individual protocols primarily in response to specific questions posed by the sponsors. While more general drug development issues, such as the *number* of trials needed or adequacy of supportive evidence for a given efficacy claim, are factors in assessing the overall adequacy of a proposed protocol, they are not considered part of the special protocol assessment program. Questions pertaining to such general drug development issues should be

discussed in routine drug development meetings and correspondence with the review or applications division and, as appropriate, with the review office.

IV. AGENCY ASSESSMENT

A. Action on the Request

After receiving a written request for special protocol assessment, the review or applications division director will decide whether the submission is appropriate for such assessment. In CDER, this decision will be based on recommendations from the clinical team leader, chemistry team leader, or pharmacology/toxicology team leader, as appropriate. In CBER, the decision will be based on the recommendations of the review team. If the division concludes that special protocol assessment is appropriate, the division will proceed with the assessment (see **Assessment of the Protocol** below). If special protocol assessment is not appropriate (i.e., the protocol does not meet the criteria for special protocol assessment), the division should notify the sponsor of the reasons for the determination as soon as possible after the Agency's receipt of the request. If the sponsor is notified by telephone or fax, a hard copy of the letter documenting the determination should follow.

B. Assessment of the Protocol

For each special protocol assessment under this program, the centers will answer any questions that are appropriate, providing comments on issues related to protocol design, study conduct and execution, data analysis, and implications for labeling. The Agency's assessment will be based primarily on the questions posed by the sponsor, the underlying data, assumptions, and information described by the sponsor, and relevant Agency policies and guidance documents. Any change in the underlying data, assumptions, and information could affect the assessment of the protocol. Comments from the review team should be sent to the sponsor in a special protocol assessment letter within 45 calendar days of receipt of the request for special protocol assessment. If the letter is faxed to the sponsor, a hard copy should follow.

1. *Revisions During Agency Assessment*

The Agency may communicate with the sponsor regarding the protocol before issuing a special protocol assessment letter. In such cases, the sponsor may choose to submit a revised protocol. If, for any reason, a sponsor submits a revised protocol while the Agency is reviewing an earlier version of the same protocol, the Agency ordinarily will not respond to the questions posed about the earlier version of the protocol and will consider the original request withdrawn. The Agency will consider a request for special protocol assessment of a revised protocol to be a new request and will act on the revised protocol within 45 days.

2. *Advisory Committee Review*

The Agency may, as necessary, seek advisory committee review of a clinical protocol or may obtain advisory review from selected advisory committee members, special Government

employees, or other consultants. In either circumstance, in lieu of a special protocol assessment letter, the sponsor should be notified within 45 calendar days after the Agency's receipt of the request for special protocol assessment that an advisory committee or selected advisory committee members will review the protocol. If known, the date of the advisory committee meeting or consultation with advisory committee members should be provided to the sponsor with the notification. If the clinical protocol will be presented to an advisory committee, the presentation should be scheduled to take place at the next *available* advisory committee meeting. A special protocol assessment letter, including comments from the review team based on advice from the advisory committee or selected advisory committee members, should be sent to the sponsor within 45 calendar days of the expert review of the protocol. If the notification or special protocol assessment letter is faxed to the sponsor, a hard copy should follow.

V. MEETINGS

If a sponsor requests a meeting with CDER or CBER after receipt of a special protocol assessment letter, the request will be handled as a request for a Type A meeting under the PDUFA goals for meeting management. This meeting will be scheduled to take place within 30 calendar days after receipt of the written request for the meeting. At the Type A meeting, the Agency representatives and the sponsor should discuss any remaining issues and uncertainties regarding the protocol. If CDER or CBER believes that meeting with a sponsor would be the best way to resolve outstanding issues regarding a special protocol assessment, the Agency may suggest that the sponsor request such a meeting. Any meeting with the sponsor should be scheduled and conducted under the policies and procedures established by CDER and CBER.

VI. DOCUMENTATION

A. Form of Documentation

All agreements and disagreements between the Agency and the sponsor regarding special protocol assessments, including Agency responses to questions about protocol design, primary efficacy endpoints, study conduct, data analysis, and the kind of labeling statements one could expect if the data are supportive and the product is approved, should be clearly documented in writing. These special protocol assessments may be documented in the special protocol assessment letter and/or the minutes of the Type A meeting. While a special protocol assessment may document the Agency's agreement that the design and planned analysis of a study adequately address objectives in support of a regulatory submission, the Agency will not necessarily agree that a specific finding (e.g., a particular p value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. Such determinations are made after review of a complete marketing application and are based on the totality of data in the application.

B. Changes in Documented Special Protocol Assessments

As stated in the PDUFA goals for special protocol assessment and agreement,

> having agreed to the design, execution, and analyses proposed in protocols reviewed under this process [i.e., carcinogenicity protocols, stability protocols, and phase 3 protocols for clinical trials that will form the primary basis of an efficacy claim], the Agency will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident.

Documented special protocol assessments should be considered binding on the review division and should not be changed at any time, except as follows.

- Failure of a sponsor to follow a protocol that was agreed upon with the Agency will be interpreted as the sponsor's understanding that the protocol assessment is no longer binding on the Agency.

- If the data, assumptions, or information provided by the sponsor in a request for special protocol assessment change, are found to be false statements or misstatements, or are found to omit relevant facts, the Agency will not be bound by any assessment that relied on such data, assumptions, or information.

- A clinical protocol assessment will no longer be considered binding if (1) the sponsor and FDA agree in writing to change the protocol or (2) the director of the review division determines that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun (section 505(b)(4)(C) of the Act). If the director of the review division makes such a determination, (1) the determination should be documented in writing for the administrative record and should be provided to the sponsor and (2) the sponsor should be given an opportunity for a meeting at which the review division director will discuss the scientific issue involved (section 505(b)(4)(D) of the Act). This meeting will be a Type A meeting under the PDUFA goals for meeting management.

C. Personnel Changes

Changes in personnel on both the Agency's review team and the sponsor's development team are common during drug development. Personal preferences of new individuals on either team should not alter any documented special protocol assessment.

VII. DISPUTE RESOLUTION

A sponsor should first seek to resolve disagreements with FDA action under the special protocol assessment program with the review or applications division. Any dispute regarding study design should be resolved prior to initiation of the trial. If the sponsor is not satisfied with the response provided by that FDA component, the sponsor may elect to pursue the Agency's procedures for formal

261 dispute resolution (21 CFR 10.75, 312.48, and 314.103).[5] However, if an advisory committee
262 evaluates a protocol as part of special protocol assessment, further review by the advisory committee
263 need not be obtained as part of dispute resolution.

[5] A draft guidance for industry, *Formal Dispute Resolution: Appeals Above the Division Level,* was made available to the public for comment in March 1999 (64 FR 13587) and is currently being finalized.